Reprinted from the American Journal of Physiology

Vol. XXXIV—May 1, 1914—No. II

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[From the Laboratory of Physiology in the Harvard Medical School]

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Received for publication March 30, 1914

IN the preceding paper of this series evidence was given to prove that stimulation of splanchnic nerves, with accompanying increase of adrenal secretion, results in more rapid clotting of blood. Recent experiments have shown that certain conditions — such as pain and emotional excitement — likely to arise in the natural life of organisms and known to be attended by nervous discharges over splanchnic courses, are also attended by increased secretion of adrenalin into the blood.[1] Does the adrenalin thus liberated have any effect on the rate of coagulation? The observations here recorded were made in order to obtain an answer to that question.

The effect of "painful" stimulation. — In experiments on the action of stimuli which in the unanaesthetized animal would cause pain, faradic stimulation of a large nerve trunk (the stump of the cut sciatic), and operation under light anaesthesia, were the methods used to affect the afferent nerves. Elliott found that repeated excitation of the sciatic nerve was especially efficient in exhausting the adrenal glands of their adrenalin content, and also that this reflex persisted after removal of the cerebral hemispheres.[2] It was to be expected, therefore, that with well-stored glands, sciatic stimulation, even in the decerebrate animal, would call forth an amount of adrenal secretion which would decidedly hasten clotting. The following case illustrates such a result:

[1] Cannon: This journal, 1914, xxxiii, p. 357.

[2] Elliott: Journal of physiology, 1912, xliv, pp. 406, 407.

Dec. 12. A cat was anaesthetized with ether at 3.45, and the left sciatic nerve was bared. Decerebration was completed at 3.57. The clotting time of the blood began to be tested six minutes later:

4.03 — 4 minutes	4.45 to .50 Stim. left sciatic
.08 — 3.5 "	.53 — 2.5 minutes
.13 — 3.5 "	.57 — 7 "
.18 — 4.5 "	5.06 — 7.5 "
.23 to .25 Stim. left sciatic	.15 to .17 Stim. left sciatic
.26 — 2.5 minutes	.17 — 4 minutes
.29 — 3.5 "	.22 — 4.5 "
.34 — 4.0 "	.27 — 5.5 "
.40 — 5.0 "	.36 — 5.5 "
	.46 — 7 "

The results obtained in this case, which were similar to results in other cases, are represented graphically in Figure 1. The

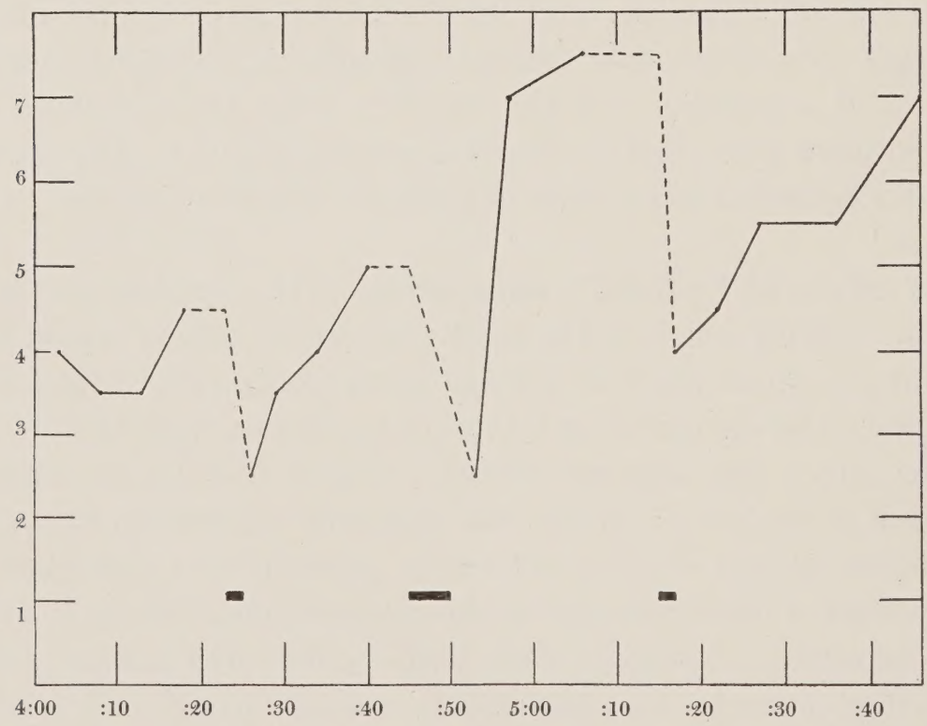

FIGURE 1. Three shortenings of coagulation time after stimulation of the left sciatic nerve, at 4.23 — .25, at 4.45 — 50 (stronger), and at 5.15 — .17.

coagulation time was becoming gradually more prolonged, but each excitation of the sciatic nerve was followed by a marked shorten-

ing. The strength of stimulation was not determined with exactness, but it is worthy of note that the current used in first and third stimulations was weaker than could be felt on the tongue, whereas that used in the second was considerably stronger, though it did not produce reflex spasms.

Mere tying of the nerve is capable of producing a marked shortening of coagulation, as the following figures show:

Oct. 21. 10.57 Cat under ether and urethane given
11.11 — 8.5 minutes
.23 — 8.5 "
.32 to .35 Left sciatic bared and tied
.37 — 1.5 minutes
.41 — 5.5 "
.50 — 7 "
12.02 — 8.5

Stimulation of the crural nerve had similar effects, reducing the clotting time in one instance from a succession of 3, 3, and 3.5 minutes to 1.5 minutes shortly after the application of the current, with a return to 3.5 minutes at the next test.

Operative procedures performed under light anaesthesia, or reduction of anaesthesia soon after operation, resulted in a remarkable shortening of the coagulation time:

Nov. 8. A cat was etherized and tracheotomized. The abdomen was then opened, and a ligature was drawn around the hepatic nerves. The operation was completed at 2.25. At 2.50 the etherization became light and the rate of clotting began to be faster:

2.50 — 6 minutes	.15 — 3.5 minutes
3.00 — 5.5 "	.20 — 4.5 "
.10 — 3.5 "	.30 — 7.5 "

Nov. 11. A female cat, very quiet, was placed in the holder at 1.55. The animal was not excited. At 2.10 etherization was begun; the animal was then tracheotomized, and the femoral artery was exposed.

2.21 — 4.5 minutes

.26 — 4.5 " Anaesthesia lessened

.32 — 3.5 " " light

.35 — Abdomen opened

.47 — 1.5 minutes

.52 — 1 "

.55 — Ligature passed around hepatic nerves

.57 — 1.5 minutes Anaesthesia light; corneal reflex present

3.02 — 3 "

.07 — 3 " Some hepatic nerves cut

.12 — 4.5 " Rest of hepatic nerves cut

.22 — 5 "

The results of this experiment are shown graphically in Figure 2.

Nov. 13. A cat was etherized at 1.55, tracheotomized, and the femoral artery laid bare. As soon as these preparations were completed, the ether was removed and anaesthesia became light. The blood clotted thus:

2.08 — 6 minutes,

.15 — 4 " Anaesthesia light

.20 — 2 "

.24 — 1 " Etherization begun again

.27 — 2.5 "

.30 — 3.5 "

.35 — 5.5 "

.50 — 5.5 "

In the foregoing and in other similar instances, a condition of surgical injury, whether just made or being made, was accompanied by more rapid clotting of blood when the degree of anaesthesia was lessened. This condition was one which, if allowed to go further in the same direction, would result in pain. Both direct electrical stimulation and also surgical operation of a nature to

give pain in the unanaesthetized animal, result, therefore, in faster clotting. It is worthy of note that after decerebration clotting apparently occurred no faster because the abdomen had been opened, although in the decerebrate state etherization was suspended. The mechanism for reflex control of the adrenals may not be higher than the corpora quadrigemina, as Elliott has shown, but the discharge from the glands seems to be more certain to occur when the cerebrum is present and is permitted even slightly to operate.

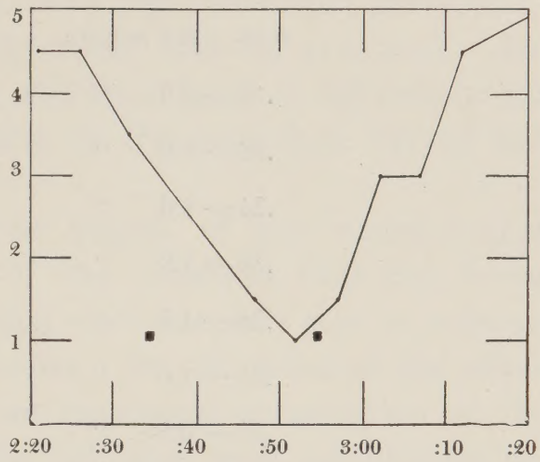

FIGURE 2. Shortening of coagulation time during an operation under light anaesthesia. At 2.35 the abdomen was opened, at 2.55 a ligature was passed around the hepatic nerves.

The effect of emotional excitement. — Reference has already been made to the emotional secretion of the adrenal glands. In their emotional reaction to being bound cats differ widely: some, especially young males, become furious; others, especially elderly females, take the experience quite calmly. This difference of attitude was used with positive results in experiments on emotional glycosuria,[1] and it seemed possible, therefore, to use it to test the effect of emotions on blood-clotting. To plan formal experiments for that purpose was not necessary, because in the ordinary course of the researches here reported, the difference in effects on the blood between the violent rage of vigorous young males and the quiet complacency of old females was early noted. Indeed the rapid clotting which accompanied excitement not infrequently made necessary an annoying wait till slower clotting would permit the use of experimental methods for shortening the process.

The animals used on November 11 and 13 (see pp. 253, 254) are examples of calm acceptance of being placed on the holder, and furthermore these animals were anaesthetized without much disturbance. As the figures indicate, from the first the clotting occurred at about the average rate.

[1] See CANNON, SHOHL, and WRIGHT: This journal, 1911, xxix, p. 280.

In sharp contrast to these figures are those obtained when a vigorous animal is angered:

Oct. 30. A very vigorous cat was placed on the holder at 9.08. It at once became stormy, snarling, hissing, biting, and lashing its big tail. At 9.12 etherizing was begun and that intensified the excitement. By 9.15 the femoral artery was tied. The clotting time of the blood for an hour after the ether was first given was as follows:

9.18 — 0.5 minute	9.43 — 1.0 minute
.19 — 1.0 "	.45 — 0.5 "
.22 — 1.0 "	.49 — 0.5 "
.24 — 1.0 "	.52 — 0.5 "
.26 — 1.0 "	.54 — 0.5 "
.28 — 1.5 "	.57 — 1.0 "
.31 — 1.0 "	10.00 — 0.5 "
.33 — 0.5 "	.02 — 0.5 "
.35 — 0.5 "	.06 — 1.0 "
.38 — 0.5 "	.09 — 0.5 "
.39 — 0.5 "	.11 — 0.5 "
.41 — 1.0 "	.13 — 1.0 "

Twenty-four observations made during the hour showed that the clotting time in this enraged animal averaged three-fourths of a minute and was never longer than a minute and a half. The clots were invariably a solid jelly. The persistence of the rapid clotting for so long a period after anaesthesia was started, may have been in part due to continued, rather light etherization, for Elliott found that etherization itself could reduce the adrenalin content of the adrenal glands.[1]

The shortened clotting did not always persist so long as in the foregoing instance. The brief period of faster clotting illustrated in the following case was typical of many:

Nov. 18. A cat that had been in stock for some time was placed on the holder at 2.13, and was at once enraged. Two minutes later

[1] ELLIOTT: *loc. cit.*, p. 388.

etherization was started. The hairs on the tail were erect. The clotting was as follows:

2.25 — 1.0 minute	.31 — 4.5 minutes
.27 — 0.5 "	.37 — 3.5 "
.28 — 2.0 "	.47 — 4.5 "

It seems probable that in this case, because of the cat's being caged near dogs, the adrenals were well-nigh exhausted previous to this experiment, and that the emotional flare-up practically discharged the glands, for repeated attempts later to reproduce the initial rapid clotting by stimulation of the splanchnic nerves was without result.

Evidence presented in previous papers of this series makes wholly probable the correctness of the inference that the faster coagulation which follows emotional excitement is due to adrenal discharge from splanchnic stimulation. In this relation the effect of severance of the splanchnics on emotional acceleration of the clotting process is of interest. The following cases are illustrative:

Oct. 29. A cat was left on the holder for 10 minutes while the femoral artery was uncovered under local anaesthesia. The blood removed was clotted in a half-minute. The animal was much excited. It was now quickly etherized and the brain pithed forward from the neck. The tests resulted as follows:

10.51 — 1.0 minute
.53 — 05. "
.55 — 0.5 "
.57 — 0.5 "
11.07 — Cut left splanchnic
.12 — " right splanchnic
.21 — 3.5 minutes
.26 — 3.5 "

The original record of this case is given in Figure 3.

Nov. 5. A cat was etherized at 2.35. At 2.39 artificial respiration by tracheal cannula was begun, the air passing through an ether bottle. The clotting occurred thus:

2.53 — 1.5 minutes
.57 — 1.5 "
3.05 — 1.5 "
.15 — 1.5 "
.25 — Both spl. cut and tied in thorax
.35 — 4.5 minutes
.55 — 4.5 "

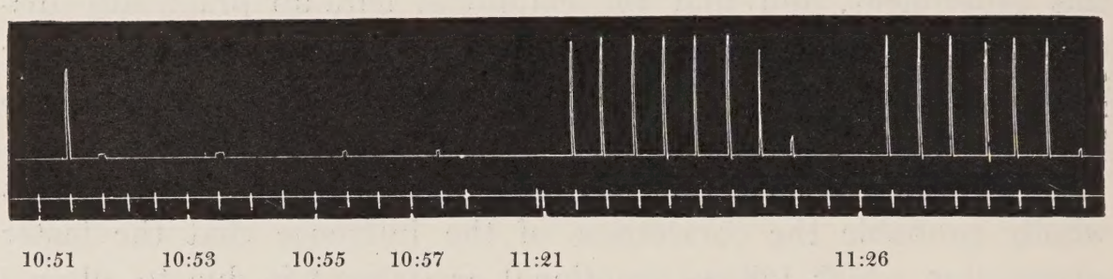

FIGURE 3. About two-thirds original size. Record of rapid clotting (less than a half-minute) after emotional excitement. At 11.07 the left, at 11.12 the right splanchnic nerves were cut; the clotting then required 3.5 minutes. The marks below the time record indicate the moments when the samples were drawn.

Nov. 7. A cat was etherized under excitement and with tail-hairs erect, at 1.55. At 2.13 the animal was showing reflexes. The figures show the course of the experiment:

2.15 — 1.5 minutes
.21 — 1.0 "
.26 — 1.0 "
.31 — 1.0 "
.36 — 1.0 "
.41 — 1.0 "
.46 — 2.0 "
.51 — 2.0 "
3.06 — 2.0 minutes
.11 — 2.5 "
.26 — Cut left spl. in thorax
.35 — " right spl. in thorax
.40 — 5.0 minutes
.45 — 5.0 "
.51 — 5.5 "

In this instance the subsequent stimulation of the splanchnic nerves resulted again in faster clotting — a reduction from 5.5 minutes to 3.5 minutes.[1] The results from this experiment are shown graphically in Figure 4.

[1] See CANNON and MENDENHALL: This journal, 1914, xxxiv, p. 245, experiment on Nov. 7.

Discussion

The data presented in this paper show that such stimulation as in the unanaesthetized animal would cause pain, and also such emotions as fear and rage, are capable of greatly shortening the coagulation time of blood. These results are quite in harmony with the evidence previously offered that injected adrenalin and

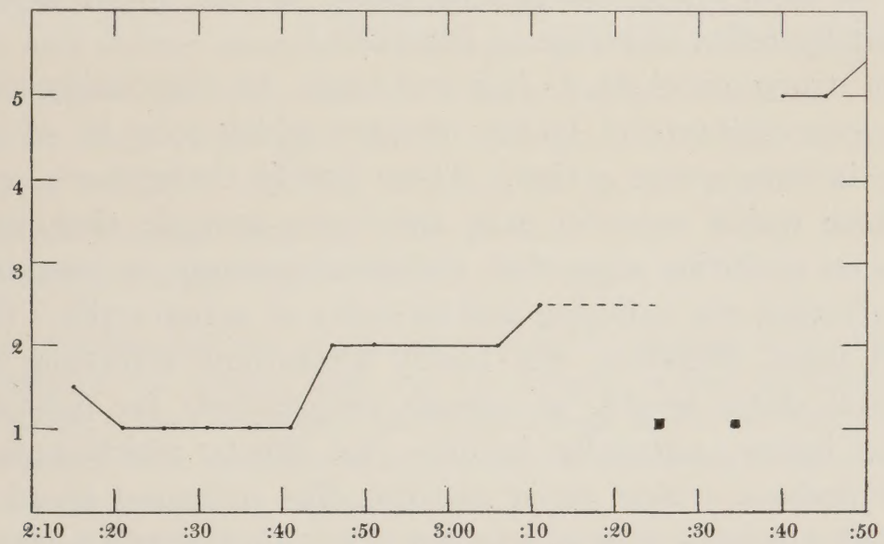

Figure 4. Rapid clotting after emotional excitement, with slowing of the process when the splanchnic nerves were cut in thorax (the left at 3.26, the right at 3.35).

secretion from the adrenal glands induced by splanchnic stimulation hasten clotting, for, as already stated, painful stimulation and emotional excitement also evoke activity of the adrenals.

In a previous paper the increase of blood sugar and the secretion of adrenalin in pain and the major emotions were interpreted as biological adaptations to conditions likely to involve, in wild life, pain and great emotion — i.e., the necessities of struggle, fighting or flight. The sugar would then serve the muscular energies, the adrenalin would aid in distributing blood to organs critically involved in the struggle, and would also abolish or minimize the effects of fatigue.[1] The more rapid clotting of blood in pain and emotional excitement may also be regarded as an adaptive process, useful to the organism. The importance of conserving the blood needs no argument. The effect of local injury in favoring the formation of a clot to seal the opened vessels

[1] See Cannon: This journal, 1914, xxxiii, p. 372.

is obviously adaptive in protecting the organism against hemorrhage. The injury that causes opening of blood vessels, however, is, if extensive, likely also to produce pain. And, as shown above, conditions producing pain increase adrenal secretion and hasten coagulation. Thus injury would be made less dangerous as an occasion for serious hemorrhage by two effects which the injury itself produces in the body, — the local effect on clotting at the region of injury and the general effect on the speed of clotting wrought by reflex secretion of adrenalin.[1]

The strong emotions, as fear and anger, are reasonably regarded as the concomitants of bodily changes which may be of utmost service in subsequent action. These bodily changes are so much like those which occur in pain and fierce struggle that, as early writers on evolution suggested, the emotions may be considered as foreshadowing the suffering and intensity of actual strife. On this general basis, therefore, the bodily alterations attending violent emotional states would, as organic preparations for fighting and possible injury, naturally involve the effects which pain itself would produce. And rapid clotting, like increased blood sugar, increased adrenalin, and an adapted circulation, would be favorable to the preservation of the organism that could best effect it.[2]

[1] The conditions under which pain and danger from hemorrhage occur together in civilization are not so frequent as to permit a ready testing on man of the ideas here propounded. It is possible that the pain of childbirth is such as to lead to adrenal discharge (the increase of blood-sugar during parturition is indicative of that), and thus to favor rapid clotting at a time when that may be important.

[2] There is evidence that asphyxia causes increased secretion of adrenalin (see CANNON: This journal, 1914, xxxiii, p. 357), and often in the course of these investigations we have noted that when respiration became impaired and the blood turned dark, clotting was faster. In a few observations, however, in which a formal attempt was made to determine the influence of asphyxia on clotting, the results were not always positive — due probably to the use of animals which had been kept for some time in conditions likely to discharge the adrenal glands.

Stewart (Journal of experimental medicine, 1912, xv, p. 547) and Hoskins and McPeek (Journal of the American Medical Association, 1913, lx, p. 1778) have reported that direct massage of the adrenal glands causes an increased secretion of adrenalin. The increase, according to the latter authors, is slight. Mr. Horace Gray and Mr. C. A. L. Binger have tried in this laboratory the

Summary

Stimulation of afferent nerves (sciatic, crural), or major operations under light anaesthesia, markedly shorten the coagulation time of blood.

Emotional excitement is the occasion for very rapid clotting (sometimes in less than a half-minute), which becomes slow (three to five minutes) when the splanchnic nerves are cut.

Pain and strong emotions have been proved to evoke secretion of the adrenal glands; and adrenalin hastens clotting. Rapid coagulation may reasonably be considered, therefore, as another instance of adaptive reaction serviceable to the organism in the injury which may accompany pain or which may follow the struggle that fear or rage may occasion.

possibility of influencing the coagulation of blood by massage of the adrenals. In one instance the clotting time was 5.5 minutes in four successive tests before massage. After massage it fell to an average of 4.6, for forty minutes. Then the glands were manipulated again, and the eight tests taken thereafter were as follows: 3.5, 4.5, 4, 4, 3.5, 4.5, 3.5, 4. In another instance massage of the glands reduced the time, after a brief prolongation, from an average of 6.1 minutes to an average of 4.7 minutes, with six tests in each group. In other cases the tests were not so favorable. Massage of the liver was without clear effect.

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